REMARKS

Upon entry of this amendment, claims 1-3, 5 and 11 are pending in the instant application. Claims 1, 3 and 11 have been amended herein. Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. Support for correcting the typographical error of "thioureido" is found at page 28, lines 22-24 and page 30, lines 12-14. Accordingly, no new matter has been added by these amendments.

I. CLAIM REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 2, 3, 5 and 11 were rejected under 35 U.S.C. §112, first paragraph for lack of written description. The Examiner states that the recited substituents "ureido" and "thoureido" lack support in the specification as originally filed. *See*, Office Action at page 2. Applicants respectfully note claim 2 does not recite substituents "ureido" and "thoureido." Applicants traverse the rejection as it applies to claims 3, 5 and 11 as amended herein.

Applicants have amended claims 3 (from which claim 5 properly depends) and 11 to correct a typographical error, and now these claims recite "ureido" and "thioureido" substituents. Applicants submit that one skilled in the art would readily recognize that "ureido" and "thioureido" substituents are urea and thiourea derivatives. Support for "ureido" and "thioureido" substituents is found throughout the instant application. For example, the specification discloses that ureido and thioureido isoxazoles can be synthesized by reacting 5-aminoisoxazoles with isocyanates and thioisocyanates. *See*, Specification at page 28, lines 22-24 and page 30, lines 12-14. Further, the 5-aminoisoxazole of the invention can be prepared from α-halo oximes by reaction with sodium cyanide. *See*, Specification at page 30, lines 10 – 12 and page 30, Scheme 6. Thus, the application describes synthesizing ureido and thioureido isoxazoles from several starting reagents. As such, Applicants contend that the specification reasonably conveys to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed and respectfully request the rejection be withdrawn.

II. CLAIM REJECTION UNDER 35 U.S.C. §102

The Examiner has rejected claims 1-3, 5 and 11 under 35 U.S.C. 102(b) as being anticipated by WO 97/28160 to Elliott ("Elliott"). The Examiner states that Elliott teaches isoxazole compounds, including methods of using the compounds to treat hypertension, encompassed by the instant claims. *See*, Office Action at pages 2 – 3. Applicants traverse the rejection as it applies to the pending claims as amended herein.

Elliott discloses isoxazole compounds substituted with Ar', *see* Elliott at page 5. Elliott defines Ar' as aromatic substituents (specifically naphthyl, furyl, oxozolyl, indolyl, pyridyl, thienyl, oxazolidinyl, thiazolyl, isothiazolyl, pyrazoiyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, or pyrimidyl) and as non-aromatic substituents (specifically morpholinyl, piperidinyl, and piperazinyl). *See* Elliott at page 7, line 27 – page 8, line 2. As amended, claim 1, and dependent claims 2-3, 5 and 11, recite a method of treating hypertension by administering isoxazole compounds, which are optionally substituted with *non-aromatic* substituents. Further, the claimed substituents do not include the non-aromatic substituents listed in Elliott (morpholinyl, piperidinyl or piperazinyl). The claimed methods of treating hypertension with the isoxazole compounds of the invention are not taught or suggested by Elliott. As such, Applicants submit that Elliott does not anticipate pending claims 1-3, 5 and 11, as amended herein, and respectfully request that this rejection be withdrawn.

III. CLAIM REJECTION UNDER 35 U.S.C. §103

Claims 1-3, 5 and 11 were rejected under 35 U.S.C. §103 as being unpatentable over WO 91/15479 to Allen ("Allen"). The Examiner states that Allen teaches isoxazole compounds, wherein the carbon adjacent to the nitrogen may be substituted with lower alkyl groups, such as methyl. Though Allen does not expressly teach isoxazole compounds with hydrogen at the carbon adjacent to the nitrogen, the Examiner asserts that one of ordinary skill would have been motivated to prepare the instantly claimed compound because it is structurally homologous. *See* Office Action at page 3. Applicants traverse the rejection as it applies to the pending claims as amended herein.

Allen discloses heterocyclic compounds containing an N-K bond, such that when K is oxygen, the compounds are isoxazoles having a complex aryl group connected to the isoxazole with an alkylene linker. Further, the compounds in Allen have R^8 bonded to the carbon adjacent

to K, and E-R^6 bonded to the carbon adjacent to the nitrogen. *See* Allen at page 4. E can be a single bond, -$NR^{13}(CH_2)_s$-, or -$S(O)_x(CH_2)_s$ where x is zero to two and s is zero to five, -CH(OH)-, -O-, -CO-. *See* Allen at page 8. Further, R^6 can be C_1-C_6-alkyl, C_2-C_5-alkenyl or C_2-C_5-alkynyl each of which can be substituted with aryl, C_3-C_7-cycloalkyl, halo, -OH, -CF_3, -CCl_3, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, NH-SO_2R^4, -$COOR^4$, -SO_2NHR^9, C_1-C_4-alkoxy, or C_1-C_4-alkyl-S. *See* Allen at page 8. Allen does not suggest hydrogen at the carbon adjacent to the nitrogen.

Amended claim 1, from which the remaining claims subject to the rejection depend, recites a method of treating hypertension by administering isoxazole compounds optionally substituted on carbon atoms with the recited non-aryl substituents. The amended claims do not permit substitution of the isoxazole with any type of aromatic substituents. Further, isoxazoles of the invention have a hydrogen substituent at the carbon adjacent to the nitrogen. Applicants submit that the compounds of the invention are not structurally homologous to the compounds in Allen and therefore not obvious in view of Allen. More specifically, Applicants submit that the disclosure in Allen is unduly broad, and that the methyl substituent on the carbon adjacent to the nitrogen and the complex aromatic substituent are structurally dissimilar to the compounds of the present invention, that there is no motivation to modify Allen and that there is no reasonable expectation of similar properties. For all of these reasons, Applicants submit that the pending claims are not obvious in view of the disclosure in Allen.

A. Overbroad Genus

Applicants contend that one skilled in the art would not have been motivated to select the claimed subgenus from the broad genus disclosed in Allen. The M.P.E.P. states that when the prior art teaches a genus, a subgenus is obvious only when one of ordinary skill in the art would have been motivated to select the claimed subgenus. *See* M.P.E.P. § 2144.08. In making this determination, the Examiner is instructed to consider the size of the genus, the express teachings, the teachings of structural similarity, the teaching of similar properties or uses, the predictability of the technology, and any other teachings. *See* M.P.E.P. § 2144.08.

Applicants submit that the disclosure in Allen is unduly broad, and does not overlap with Applicants' compounds, such that one of ordinary skill in the art would not have been motivated to select the subgenus as claimed in the instant invention. In particular, Allen discloses

isoxazole, isothiazole and pyrazole compounds with a number of possible substituents, including a required complex aromatic moiety. *See* Allen at pages 4-14. Allen provides no teaching or suggestion that the isoxazole compounds are better anti-hypertensives than either the isothiazole or the pyrazole, and no mention of which type of substituents, other than the requisite complex aryl moiety, are desirable. In fact, Allen discloses no examples demonstrating the relative anti-hypertensive properties of these compounds. Further, Allen only provides broad genera of preferred compounds. *See* Allen at page 16. All subgenus formulae contain the complex aryl moiety, and little or no suggestion of how to select the identity of the other substituents. Consequently, Applicants contend that Allen is too broad and unrelated to render the instantly claimed compounds obvious.

B. Structural Similarity

The M.P.E.P. states that a *prima facie* case of obviousness is made when compounds have very close structural similarities and similar utilities. *See* M.P.E.P. § 2144.09. Examples of very close structural similarities include adjacent homologues and structural isomers, *see* In re Wilder, 563 F.2d 457 (CCPA 1977), stereoisomers, *see* In re May, 574 F.2d 1082 (CCPA 1978), and acid and ethyl esters. Applicants submit that the compounds in the amended claims are not structurally homologous to the compounds in Allen.

1. Complex Aromatic Substituent

The Examiner has asserted that one of ordinary skill would have been motivated to prepare the instantly claimed compounds, wherein the carbon adjacent to the nitrogen may be substituted with hydrogen, because it is structurally homologous to the compounds disclosed in Allen, wherein the carbon adjacent to the nitrogen may be substituted lower alkyl groups. Office Action at page 3. In contrast, Applicants submit that the compounds in the amended claims are not structurally homologous to the compounds in Allen, as the instant claims require isoxazole compounds optionally substituted on carbon atoms with non-aryl substituents. *See* In re Hoch, 428 F.2d 1341 (CCPA 1970). Allen does not disclose homologues, structural isomers, or stereoisomers.

Rather, Allen discloses compounds having a complex aryl substituent, that includes two aromatic moieties, connected by an alkylene linker. Aromatic compounds are a unique class of compounds that have a number of characteristics, including planarity, stability and different reactive properties relative to non-aromatic compounds. None of the instant compounds contain aromatic substituents, much less the complex substituent as described by Allen. Further, none of the substituents in the instant claims are bioisosteric for the aromatic substituent in Allen, nor do they possess many of the characteristics of such an aromatic compound. As such, Applicants submit that the compounds in the amended claims are not structurally homologous to the compounds in Allen.

2. Hydrogen on Carbon Adjacent to the Nitrogen

Applicants further submit that one of ordinary skill would not have been motivated to prepare the instantly claimed compounds, because the instantly claimed compounds with hydrogen on the carbon adjacent to the nitrogen are not structurally homologous to the compounds disclosed in Allen, wherein the carbon adjacent to the nitrogen may be substituted lower alkyl groups. Applicants note that the MPEP requires very close structural similarity to establish prima facie obviousness. Allen does not disclose homologues, structural isomers, or stereoisomers of the hydrogen-containing compounds claimed in the instant application. At best, the substituent on the carbon adjacent to the nitrogen in the Allen compounds is lower alkyl, *i.e.*, a methyl group. The hydrogen substituent in the instant claims is not bioisosteric for the lower alkyl substituents in Allen. Consequently, Applicants submit that the claimed compounds are not structurally similar to the compounds disclosed in Allen.

C. Motivation to Modify

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a prior art reference must establish that: (1) the prior art contains a suggestion or motivation to modify the prior art reference in such a way as to achieve the claimed invention; (2) there must be a reasonable expectation of success; and (3) the prior art must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. In re Napier, 55 F.3d 610 (Fed. Cir.

1995). The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Laskowski, 871 F.2d 115 (Fed. Cir. 1989). Applicants submit that the prior art does not suggest or motivate the modification of Allen to result in the instantly claimed compounds.

1. Complex Aromatic Substituent

Applicants submit that one of ordinary skill in the art reading Allen would not be motivated to modify the compounds of Allen, containing a complex aromatic substituent, to arrive at the isoxazoles of the instant invention. In particular, Applicants submit that because Allen only discloses heterocyclopentanes substituted with a complex aromatic substituent, it actually teaches away from replacing the aromatic substituent with a non-aromatic substituent.

Allen discloses a broad genus of substituted heterocyclopentanes having heteroatoms N, K (*e.g.*, O in isoxazoles), and 3 carbon atoms. The carbon adjacent to the nitrogen can be substituted with the substituents R^6. Similarly, the carbon adjacent to the oxygen can be substituted with the substituents R^8. However, the other carbon of the ring can only be substituted with the complex aromatic substituent. While the other positions are open for a variety of substitutions, Allen requires a complex aromatic substituent. Consequently, Applicants contend that one of ordinary skill in the art would not be motivated to modify that substituent.

Further, based on the correlation between the anti-hypertensive function and the presence of the aromatic substituent, Applicants submit that Allen teaches away from replacing the aromatic substituent. As discussed in the Background of the Invention, Allen relates to the use of Angiotensin II antagonists as anti-hypertensives. *See* Allen at pages 2-3. Further, Allen discusses recent disclosures of non-peptide Angiotensin II antogonists that are heterocyclopentanes "which are generally bonded through a lower alkyl bridge to a substituted phenyl." Allen at page 3. Allen then proceeds to disclose a broad genus of substituted heterocyclopentanes with a complex aromatic substituent cited by the Examiner. The Background discusses aromatic substituents connected with an alkylene linker and the Detailed Description only discloses the complex aromatic substituent connected to the heterocyclopentane with an alkylene linker. Applicants submit that one of ordinary skill in the art would not be motivated to replace the complex aromatic substituent with a non-aromatic substituent, given

Allen's discussion of the functional characteristics of compounds with substituted phenyls and subsequent disclosure of additional compounds with such structure.

2. Hydrogen on Carbon Adjacent to the Nitrogen

Applicants submit that one of ordinary skill in the art reading Allen would not be motivated to modify the teaching of Allen such that the carbon adjacent to the nitrogen may be substituted with hydrogen, as taught by the instant application, rather than with lower alkyl groups, as disclosed in Allen. More specifically, Allen discloses that the carbon adjacent to the nitrogen contains a linker consisting of either a bond, a nitrogen-containing linker, or a sulfur-containing linker and discloses that both the nitrogen-containing linker and the sulfur-containing linker can be multiple lengths and contain multiple substituents. Allen provides no teaching or suggestion to choose a bond. *See* Allen at page 8.

Further, Allen discloses that **E** is preferably a linker or bond that connects to $\mathbf{R_6}$, an optionally-substituted $C_{1\text{-}6}$ alkyl, $C_{2\text{-}5}$ alkylene or $C_{2\text{-}5}$ alkynyl, which is preferably n-propyl, n-butyl, methyl, ethyl, or CH_2-S-CH_3. *See* Allen at page 16. However, Allen provides no teaching or suggestion to replace any of these preferred substituents with a hydrogen. Applicants submit that one of ordinary skill in the art would not be motivated to modify the teachings of Allen to reach the isoxazole compounds of the present invention, which are optionally substituted on the carbon adjacent to the nitrogen with hydrogen and optionally substituted at the remaining carbon atoms with non-aryl substituents.

D. Properties

A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 947 F.2d at 493. Moreover, "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988). Finally, "[a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make the compound, in the expectation that compounds similar in structure will have similar

properties." In re Payne, 606 F.2d 303, 313 (CCPA 1979). Applicants submit that one of ordinary skill in the art would not reasonably expect the instantly claimed compounds to have the same properties as the compounds of Allen.

1. Complex Aromatic Substituent

Applicants submit there is no reasonable expectation that the compounds disclosed in Allen containing a complex aryl substituent would have the same properties as the compounds without an aromatic substituent in the claims as amended. More specifically, the presence of at least two rigid, planar phenyl groups in the complex aromatic substituent suggests different steric interactions with a biological target, and thus different reactivity and/or effectivity as a therapeutic agent than expected with a compound devoid of aromatic substituents. Additional considerations include hydrophobicity and potential for intermolecular interactions, such as hydrogen bonding. Allen provides no teaching or suggestion that the aryl substituent creates similar functional properties as possessed by a compound without any aryl moieties, nor does Allen provide the identity of any substitutions on the phenyl groups that would create functional properties similar to the compounds of the pending claims as amended. Applicants submit based on the foregoing that one skilled in the art would not expect the compounds in the pending claims as amended to have anti-hypertensive properties based on the disclosure in Allen.

2. Hydrogen on Carbon Adjacent to Nitrogen

Applicants further submit there is no reasonable expectation that compounds with a lower alkyl on the carbon adjacent to the nitrogen as disclosed in Allen would have the same properties as the compounds in the claims as amended, which have a hydrogen on the carbon adjacent to the nitrogen. More specifically, the presence of the larger methyl group can result in different steric interactions with a biological target. As the carbon adjacent to the nitrogen sp^2 hybridized, is double-bonded to the nitrogen, the geometry around the carbon is trigonal planar, so there is no rotation about the bond between the carbon and the adjacent nitrogen. As such, the substituent on the carbon is geometrically fixed and the substituent bonded to this carbon is also geometrically fixed. Consequently, the steric effect of substitutions on this carbon is more important relative to an sp^3 carbon. One of ordinary skill in the art will recognize that a methyl group provides more steric bulk than a hydrogen. Thus, Applicants submit that a person of

ordinary skill would have no reasonable expectation of similar properties for compounds with a hydrogen rather than an alkyl on the carbon adjacent to the nitrogen.

CONCLUSION

As discussed *supra*, Applicants submit that the compounds disclosed in Allen are not structurally similar to the compounds in the pending claims as amended and further submit that one of ordinary skill in the would not be motivated to modify the teaching of Allen to reach the present invention nor would one skilled in the art expect the compounds of Allen to have the same properties as the compounds of the claimed invention. As a result, Applicants submit that the claims as amended are not obvious in view of Allen and respectfully request the Examiner withdraw the present rejection.

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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